REMARKS

In the Office Action dated September 25, 2002, Examiner Davis imposed a restriction requirement under 35 U.S.C. §121 against claims 1-23 and required that an election be made between one of the following groups:

> 1. (Group 1-14) includes claims 1-3, 5-11 and 23 drawn to a method for reducing induced apoptosis by the interaction of calmyrin (having the amino acid sequence recited in SEQ ID NO 2) which is mutated in the EF calcium binding hands and/or the N terminal of the amino acid sequence with presenilin 2 (SEQ ID NO: 1) that can include the wild type or a mutated version, wherein the mutations in the presenilin 2 is at amino acid residues 287, 288 and/or 297;
>
> 2. (Group 15-28) includes claims 1-3, 4, 5-11 drawn to a method for reducing induced apoptosis by the interaction of calmyrin (having the amino acid sequence recited in SEQ ID NO 2) which is mutated in the EF calcium binding hands and/or the N terminal of the amino acid sequence with presenilin 1 (SEQ ID NO: 3) that can include the wild type or a mutated version, wherein the mutations in the presenilin 2 is at amino acid residues 287, 288 and/or 297;
>
> 3. (Group 29) includes claim 12 drawn to a product wherein that product is the mutated calmyrin having a mutation in at least one calcium binding EF hand of SEQ ID NO: 2.
>
> 4. (Group 30-33) includes claims 13-16 drawn to the nucleic acid molecule encoding the mutant calmyrin of the present invention;
>
> 5. (Group 34) includes claim 17 drawn to a product wherein that product is the mutated calmyrin having a mutation in at least one amino acid penultimate N-terminal residue; and
>
> 6. (Group 35-38) includes claims 18-22, drawn to a mutant of presenilin 2 having mutations at residue 287, 288 and/or 297.

The Office concludes that the requirement for restriction is proper for the following reasons:

> "Inventions (1-28) and (29-38) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can the process for using the product as claimed can be practiced with another different product or (2) the product as claimed can be used in a materially process of using that product (M.P.E.P. 806.05 (h). In this instant case, a polypeptide could be used for several purposes, e.g. for

biochemical assay, for making and for making an affinity column to purify its antibodies; a DNA sequence used for the detection of similar DNA or RNA sequences, for making an expression vector, and for producing its encoded protein.

The methods of groups 1-28 are distinct from each other because they differ at least in objectives, method steps, reagents and/or dosages, and/or schedules response variables and criteria for success.

The products of groups 29-38 as disclosed are structurally distinct.

The species are distinct because they are structurally distinct.

Because these inventions are distinct for the reasons given above acquired a separate status in the art as shown by their different classification and/or recognized divergent subject matter, restriction for examination purposes is proper."

Applicants believe there would be a great economy of cost and effort on the part of the Office, and certainly to the applicants, if the closely related subject matter of claim 12 and 17 were examined together in this one application. Applicant maintains the subject matter of both these claims, define, but one invention, and do not possess sufficient differences to warrant issuance of separate patents. Likewise, the interdependence of the product claims and the method of using the calmyrin protein are confirmed --indeed, it is mandated-- by virtue of the fact that the description requirements of 35 U.S.C. §112 compel disclosure of different aspects of the invention in the one application which applicants have filed.

In addition, the courts have recognized that it is in the public interest to permit applicants to claim several aspects of their invention together in one application, as the applicants have done herein. The CCPA has observed:

> We believe the constitutional purpose of the patent system is promoted by encouraging applicants to claim, and therefore to describe in the manner required by 35 U.S.C. §112 all aspects as to what they regard as their invention, regardless of the number of statutory classes involved. *In re Kuehl,* 456 F.2d 658, 666, 117 U.S.P.Q. 250, 256 (CCPA 1973).

This interest is consistent with the practical reality that a sufficiently detailed disclosure supporting claims to one aspect of an invention customarily is sufficient to support claims in the same application to other aspects of the invention.

It is vital to all applicants that restriction requirements issue only with the proper statutory authorization, because patents issuing on divisional applications that are filed to prosecute claims that the Examiner held to be independent and distinct can be vulnerable to legal challenges alleging double patenting. The third sentence of 35 U.S.C. §121, which states that a patent issuing on a parent application "shall not be used as a reference" against a divisional application or a patent issued thereon, does not provide comfort to applicants against such allegations. The Court of Appeals for the Federal Circuit has declined to hold that §121 protects a patentee from an allegation of same-invention double patenting, *Studiengesellschaft Kohle mbH v. Northern Petrochemical Co.*, 784 F.2d 351, 355, 228 U.S.P.Q. 837, 840 (Fed. Cir. 1986); and in *Gerber Garment Technology Inc. v. Lectra Systems Inc.*, 916 F.2d 683, 16 U.S.P.Q. 2d 1436 (Fed. Cir. 1990) that court held that §121 does not insulate a patentee from an allegation of "obviousness-type" double patenting, and in fact affirmed the invalidation on double patenting grounds of a patent that had issued from a divisional application filed following a restriction requirement. Furthermore, it is far from clear that the step of filing a terminal disclaimer is available to resolve a double patenting issue that arises after the issuance of patent on the divisional application.

All these considerations indicate that the imposition of a restriction requirement with inadequate authority can lead to situations in which an applicant's legitimate patent rights are exposed to uncertainty and even extinguished. Accordingly, to protect a patentee's rights and to serve the public's interest, the Examiner is not to require restriction in cases such as the present application wherein various aspects of a unitary invention are claimed.

In view of the foregoing discussion, reconsideration for the withdrawal of the requirement for restriction is courteously requested. In the event the requirement is adhered to, applicants provisionally elect with traverse, the invention of Group 29, (claim 12), for further examination on the merits.

In accordance with Office guidelines recited in MPEP Section 821.04, when elected product claims 12 and 17 (if claim 17 is rejoined with claim 12 in a single product group) are found to recite

patentable subject matter then all method claims using the product of claims 12 and 17 may be rejoined with the provisionally withdrawn method of use type claims and examined in this one application provided the method of use claims recite the product found to be patentable during examination of the elected invention. Thus understood, applicants request that when products claim 12 and 17 are found to recite patentable subject matter, non-elected claims 1-11 and 23-24 should be taken up for examination. Accordingly, non-elected method claims 1-11 and 23-24 presented in this paper have been amended so that the product in the method claims corresponds to the claims 12 and 17.

ELECTION OF SPECIES PURSUANT TO 35 U.S.C. 121

In response to the requirement for election of species, the applicants elect the following species:

(1) The applicants elect with traverse the a mutant species with a mutation in the amino acid residues at position 116-128 in the EF-N calcium binding hand. The elected species reads on the linking claim 1 and new claim 24, and claims 2-3, 4, 5-11 and 23-24. It is to be understood that this election is made with the proviso that (a) the requirement will be withdrawn upon the finding of an allowable linking claim; and (b) any non-elected species readable on an allowed linking claim will also be found allowable.

Fees Payable

One new independent claim has been added beyond the number for which a fee has previously been paid, resulting in an added claim fee of $42.00. The U.S. Patent and Trademark Office is hereby authorized to charge the amount of $42.00 for one additional independent claim to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

Respectfully submitted,

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APPENDIX A

Please amend claims 1, 3-5, 12-13, 17-18 and 23 as follows:

1. A method to reduce induced apoptosis mediated by protein-protein interaction, the method comprising:

inhibiting interaction of presenilin 2 comprising an amino acid sequence as set forth in SEQ ID NO: 1 with a calcium-binding [myristoylated protein having an homology to calcineurin] protein comprising an amino acid sequence set forth in SEQ ID NO: 2.

3. The method according to claim 2, wherein the calcium-binding [myristoylated] protein is a human protein.

4. The method according to claim 3, wherein the calcium-binding [myristoylated] protein has reduced interaction with presenilin 1 having an amino acid sequence set forth in SEQ ID NO: 3 relative to the interaction with presenilin 2.

5. The method according to claim 3, wherein inhibiting the interaction between the presenilin 2 and calcium-binding protein is facilitated by substitution of <u>at least one</u> amino acid residue selected from the group consisting of 287, 288 and 297 of SEQ ID NO: 1.

12. A <u>purified</u> [substantially pure] mutant calcium-binding protein comprising an amino acid sequence as set forth in SEQ ID NO: 2 and having a substitution of at least one amino acid residue in at least one calcium-binding EF-hand of SEQ ID NO: 2.

13. An isolated [and purified] nucleic acid molecule encoding a mutant calmyrin protein, the mutant protein comprising at least one amino acid residue substitution at position 2, 127 or 172 of SEQ ID NO: 2.

17. A substantially pure mutant calcium-binding protein having an amino acid sequence as set forth in [comprising] SEQ ID NO: 2 having a substitution of at least one amino acid penultimate N-terminal residue.

18. An isolated and purified nucleic acid molecule encoding a mutant of human presenilin 2 protein [(SEQ ID NO.: 1)], the mutant comprising at least one amino acid substitution at positions 287, 288 or 297 of SEQ ID NO: 1.

23. A method of reducing apoptosis in neuronal cells comprising:
administering a calcium-binding [myristoylated] protein [having an homology to calcineurin comprising the amino acid sequence depicted in SEQ ID NO.: 2,]in a sufficient amount to effect protein-protein interaction with presenilin 2 [comprising the amino acid depicted in SEQ ID NO: 1], wherein [the amino acid sequence depicted in SEQ ID NO.: 2 contains] the calcium-binding protein comprises at least one substitution in the amino acid residues in the calcium-binding EF-hands [and/]or in a penultimate N-terminal residue of SEQ ID NO: 2.

APPENDIX B

All pending claims

1. A method to reduce induced apoptosis mediated by protein-protein interaction, the method comprising:

inhibiting interaction of presenilin 2 comprising an amino acid sequence as set forth in SEQ ID NO: 1 with a calcium-binding protein comprising an amino acid sequence set forth in SEQ ID NO: 2.

2. The method according to claim 1, wherein the presenilin 2 is a human protein.

3. The method according to claim 2, wherein the calcium-binding protein is a human protein.

4. The method according to claim 3, wherein the calcium-binding protein has reduced interaction with presenilin 1 having an amino acid sequence set forth in SEQ ID NO: 3 relative to the interaction with presenilin 2.

5. The method according to claim 3, wherein inhibiting the interaction between the presenilin 2 and calcium-binding protein is facilitated by substitution of at least one amino acid residue selected from the group consisting of 287, 288 and 297 of SEQ ID NO: 1.

6. The method according to claim 5, in which the proline residue at position 287 is substituted by threonine.

7. The method according to claim 5, in which the alanine residue at position 297 is substituted by threonine.

8. The method according to claim 3, wherein inhibiting the interaction between the presenilin 2 and calcium-binding protein is facilitated by substitution of at least one

amino acid residue in the calcium-binding EF-hands of SEQ ID NO: 2, wherein the calcium-binding hands includes amino acid residues at positions 116 to 128 and 161 to 173 of SEQ ID NO: 2.

9. The method according to claim 8, wherein at least one acidic residue in the EF-hands is substituted with its amine counterpart.

10. The method according to claim 8, wherein at least one N-terminal residue is substituted at a position 1 to 3 of SEQ ID NO: 2.

11. The method according to claim 10, wherein an N-terminal glycine is substituted by alanine.

12. A purified mutant calcium-binding protein comprising an amino acid sequence as set forth in SEQ ID NO: 2 and having a substitution of at least one amino acid residue in at least one calcium-binding EF-hand of SEQ ID NO: 2.

13. An isolated nucleic acid molecule encoding a mutant calmyrin protein, the mutant protein comprising at least one amino acid residue substitution at position 2, 127 or 172 of SEQ ID NO: 2.

14. An expression vector comprising the nucleic acid molecule of claim 13.

15. A host cell transformed with the expression of vector of claim 14.

16. The expression vector according to claim 14, wherein the amino acid substitution is selected from the group consisting of G2A, D127N, and E172Q.

17. A substantially pure mutant calcium-binding protein having an amino acid sequence as set forth in SEQ ID NO: 2 having a substitution of at least one amino acid penultimate N-terminal residue.

18. An isolated and purified nucleic acid molecule encoding a mutant of human presenilin 2 protein, wherein the mutant comprising at least one amino acid substitution at positions 287, 288 or 297 of SEQ ID NO: 1.

19. An expression vector comprising the nucleic acid molecule of claim 18.

20. A host cell transformed with the expression of vector of claim 18.

21. The host cell according to claim 20, wherein the host cell is a bacterial cell, insect cell, plant cell or animal cell.

22. The expression vector according to claim 18, wherein the amino acid substitution is selected from the group consisting of P287T, I288L and A298T.

23. A method of reducing apoptosis in neuronal cells comprising:
administering a calcium-binding protein in a sufficient amount to effect protein-protein interaction with presenilin 2, wherein the calcium-binding protein comprises at least one substitution in the amino acid residues in the calcium-binding EF-hands or in a penultimate N-terminal residue of SEQ ID NO: 2.

24. (New) A method to reduce induced apoptosis mediated by protein-protein interaction, the method comprising:
inhibiting interaction of presenilin 2 comprising the amino acid sequence as set forth in SEQ ID NO: 1 with calmyrin protein comprising the amino acid sequence as set forth in SEQ ID NO: 2, wherein inhibiting the protein-protein interaction is effected by at least one mutation selected from the group consisting of:

1) substituting at least one amino acid residue at position 287, 288 or 297 of SEQ ID NO: 1;

2) substituting at least one amino acid residue in the calcium-binding EF-hands of SEQ ID NO: 2, wherein the calcium-binding hands include amino acid residues at positions 116 to 128 or 161 to 173 of SEQ ID NO: 2;

3) substituting at least one N-terminal residue at positions 2 or 3 of SEQ ID NO: 2; and

4) substituting at least one amino acid residue at position 2, 127 or 172 of SEQ ID NO: 2.

This confirms receipt of:

Response to September 25, 2002 Office Action in U.S. Patent Application No. 09/878,454

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